REMARKS

INTRODUCTION:

In accordance with the foregoing, claims 13 and 24 have been amended. No new matter is being presented, and approval and entry are respectfully requested.

Claims 13-15 and 24-26 are pending and under consideration. Reconsideration is respectfully requested.

REJECTION UNDER 35 U.S.C. §112:

In the Office Action, at pages 2-4, numbered paragraphs 2A-2D, claims 13-15 and 24-26 were rejected under 35 U.S.C. §112, second paragraph, for the reasons set forth therein. This rejection is traversed and reconsideration is requested.

2A. The Examiner submits that the two additional steps are unrelated to the other steps. It is respectfully submitted that the rmsd values are used to determine a degree of similarity, as noted on page 4, line 27 through p. 5, line 5 of the specification:

> When the researcher searches the similar three-dimensional structure, an r.m.s.d (root mean square distance) value is used as a scale of the similarity of the three-dimensional structures of the substances. The r.m.s.d value is a value expressing a square root of a mean square distance between the corresponding elements constituting the substances. Empirically, the substances are thought to be exceedingly similar to each other in the case where the r.m.s.d value between the substances is not greater than 1Å. (emphasis added)

Hence, a plurality of subsets are obtained for the second point set, a combination of correspondence based on a restriction condition between the elements of the first set and the elements of the second set are generated, a rmsd is calculated for the elements that have a combination of correspondence, the rmsd values are used to determine spatial similarity of the two groups of elements, and if the spatial similarity is greater than or equal to a predetermined threshold degree, a function of the first group is substantially equivalent to the function of the second group. That is, as set forth in the following generalized operations, which are listed more generally in order to help clarify that the operations are related, and each is based on the previous operations:

Divide into subsets-Now have **two sets of subsets (known and unknown)**

↓

Generate **candidates** for combination of correspondence **from unknown subsets with respect to known subsets based on restriction**

↓

Calculate **rmsd** for candidates

↓

Determine **degree of spatial similarity between each candidate and known subset** (use rmsd)

↓

If degree of spatial similarity ≥ threshold, corresponding candidate has same function as known subset

Thus, it is respectfully submitted that the operations are related, the previous operations are not irrelevant, and each operation is, in fact, based upon the previous operation, and the "outputting" is based on comparing the degree of spatial similarity determined in the previous operation with a threshold value.

Hence, it is respectfully submitted that, in claims 13 and 24, the two additional operations "determining" and "outputting," together with the remaining operations, particularly point out and distinctly claim the subject matter which applicants regard as the invention under 35 U.S.C. §112, second paragraph. Thus, claims 13 and 24 are submitted to be definite under 35 U.S.C. §112, second paragraph. Since claims 14-15 and 25-26 depend from claims 13 and 24, respectively, claims 14-15 and 25-26 are submitted to be definite under 35 U.S.C. §112, second paragraph for at least the reasons claims 13 and 24 are definite under 35 U.S.C. §112, second paragraph.

2B. The Examiner submits that the meanings of the terms "function," "substantially equivalent," "function for a sequence of atoms," and "function for a sequence of atomic groups" is not clear.

It is respectfully submitted that the meanings of the above terms are clear to one skilled in the art. For example, on page 5, line 36 through page 6, line 18, the specification recites:

> Further, it is necessary to study the preexisting substances in order to produce the new substance. For instance, in the case where the heat resistance of a certain substance is preferably strengthened, a structure commonly existing among the strong heat resisting substances is determined, and such a structure is added to a newly produced substance to thereby strengthen the function of the substance. To this end, such a function is required as to retrieve the necessary structure from the data base. However, the researchers are presently studying the necessary structure from the data base, by trial and error, using the computer graphic system for the aforementioned reasons. (emphasis added)
>
> As described above, the operators are compelled to graphically display the three-dimensional structure of the substance they want to analyze using the graphic system, and to analyze by visual comparison with other molecules on a screen, superposition, and like operations. (emphasis added)

Hence, as set forth in Merriam Webster's On-line dictionary, a function refers to: "the action for which a person or thing is specially fitted or used or for which a thing exists:

PURPOSE." Thus, it is known to those skilled in the art that a particular function may be related to a structure in a substance.

It is respectfully submitted that the Examiner has generated an example for which there is no basis: "For example, if 3-D coordinates of an atomic group of a silicon semiconductor correlates with 3-D coordinates of an atomic group of a nucleic acid, what kind of function is determined to be 'substantially equivalent'." There is no such example, and as such, applicants cannot respond to the Examiner's uncorroborated hypothetical example. That is, it is known to those skilled in the art that if a group of atoms in one biological substance is structurally similar to a group of atoms in another biological substance, the two groups of atoms may generally have a similar function. Hence, those skilled in the art would not be comparing a biological substance with, for example, a silicon semiconductor substance, but rather would be comparing a biological substance with another biological substance.

For clarity, claims 13 and 24 have been amended to insert the terminology "biological" immediately before the terms "substance" and "substances."

As noted on page 2, line 7 through page 3, line 4 of the specification:

> A basic technique in extracting the biological information is to compare the sequences. This is because it is considered that a similarity is found in the biological function if the sequences are similar. Accordingly, by searching a data base of known sequences whose functions are known for a sequence similar to an unknown sequence a homology search for estimating a function of an unknown sequence, and an alignment such that a sequence is rearranged so as to maximize the degree of analogy between the compared sequences when researchers compare the sequences are presently studied. (emphasis added)

> Further, it is considered that a region of the sequence, in which a function important for the organism is coded, is perpetuated in the evolution process. For instance, a commonly existing sequence pattern (region) is known to be found when the amino acid sequences in proteins having the same function are compared between different types of organisms. This region is called a motif. Accordingly, if it is possible to extract the motif automatically, the property and function of the protein can be shown by finding which motif is included in the sequence. Further, the automatic motif extraction is applicable to a variety of protein engineering fields such as strengthening of the properties of the preexisting proteins, addition of functions to the preexisting proteins, and synthesis of new proteins. As described above, it can be considered as an effective means in extracting the biological information to extract the motif out of the amino acid sequence. However, the extracting method is not yet established, and the researchers currently decide manually which part is a motif sequence after the homology search and alignment. (emphasis added)

Thus, it is respectfully submitted that "a sequence" of atoms or of atomic groups is known to those skilled in the art. As noted above, a "function" for a "sequence" of atoms or atomic groups is understood by one skilled in the art.

In addition, as noted above, those skilled in the art recognize that a commonly existing sequence pattern is found in proteins having the same function. Hence, such commonly existing

sequences would be said to be "substantially equivalent."

Hence, it is respectfully submitted that the meanings of the terms "function," "substantially equivalent," "function for a sequence of atoms," and "function for a sequence of atomic groups" are clear to one skilled in the art, and that claims 13 and 24 are definite under 35 U.S.C. §112, second paragraph.

2C. The Examiner seems concerned with the added operation of "determining a degree of spatial similarity." As noted above, the specification, page 2, lines 7-11: "A basic technique in extracting the biological information is to compare the sequences. This is because it is considered that a similarity is found in the biological function if the sequences are similar." Hence, a degree of spatial similarity is determined in the present invention to determine a spatial similarity value to compare with a threshold value. As is known to those skilled in the art, the spatial similarity is based on the rmsd, as noted on page 4, line 27 through page 5, line 5:

> When the researcher searches the similar three-dimensional structure, an r.m.s.d (root mean square distance) value is used as a scale of the similarity of the three-dimensional structures of the substances. The r.m.s.d value is a value expressing a square root of a mean square distance between the corresponding elements constituting the substances. Empirically, the substances are thought to be exceedingly similar to each other in the case where the r.m.s.d value between the substances is not greater than 1 Å. (emphasis added)

When the degree of spatial similarity of the first and second structure is greater than or equal to the predetermined threshold degree of similarity, the functions of the first structure (a sequence of atoms or atomic groups of atoms) of the target molecule and of the second structure (a sequence of atoms or atomic groups of atoms) of the known molecule are substantially equivalent, as is recited, for example, on page 40, line 16 through page 41, line 5 of the specification:

> FIG. 25 shows the results obtained when a spatially similar portion (a single site) is searched for based on the order of amino acid sequence using the Ca^{2+} binding site 81-108 of calmodulin as a probe. FIG. 25 indicates that the amino acid sequence numbers 96-123 in troponin C correspond to the Ca^{2+} binding sites 81-108 in calmodulin. These results are in agreement with the biochemically experimented results. FIG. 26 shows the results obtained when spatially similar portions (a plurality of sites) are searched for based on the order of amino acid sequence using Ca^{2+} binding site 81-108 and 117-143 in calmodulin as probes. FIG. 26 indicates that the amino acid sequence numbers 96-123 and 132-158 in troponin C correspond to the Ca^{2+} binding sites 81-108 and 117-143 in calmodulin. These results are in agreement with the biochemically experimented results, too. By using the apparatus of the present invention as described above, correspondence among the constituent elements of substances can be calculated in a manner such that the r.m.s.d. values are minimized in the three-dimensional structures of the substances. By displaying the corresponding portions in a superposed manner, therefore, it becomes possible to display the substances in a superposed manner in an optimum condition. (emphasis added)

On page 42, lines 15-35, the specification recites how spatial similarity is computed:

> The similarity calculation unit 88 calculates optimum superposition of three-dimensional structures. At this moment, there are provided a function for retrieving spatially similar portions based on the order of amino acid sequence that constitutes a protein, and function for retrieving spatially similar portions irrespective of the order of amino acid sequence. In retrieving the spatially similar portions based on the order of amino acid sequence, amino acids constituting the protein can be grasped as an ordered set whose elements are ordered according to the numbers of amino acid sequence, and therefore similar portions can be calculated based on the methods described in section 1, subsections (2), (3), (4), (5) and (6). By grasping the amino acid simply as a nonordered set, furthermore, it is possible to calculate spatially similar portions irrespective of the order of amino acid sequence relying upon the systems mentioned in section 1, subsections (1), (3), (4), (5) and (6). (emphasis added)

For example, examples of retrieved results of a histidine series and a serine active series as shown in FIGs. 39A and 39B, as recited on page 52, lines 18-28 of the specification:

> FIG. 39A shows the retrieved results of histidine active sites of elastase with the histidine active sites (36-41) of trypsin as probes. It will be understood that 41-46 of elastase correspond to the active sites 36-41 of trypsin. FIG. 39B shows the retrieved results of serine active sites of elastase with serine active sites (175-179) of trypsin as probes from which it will be understood that 186-190 of elastase correspond to the active sites 175-179 of trypsin. These results are in agreement with the results obtained through biochemical experiments. (emphasis added)

Hence, it is respectfully submitted that determining spatial similarity is clear to one skilled in the art. Thus, claims 13 and 24 are submitted to be definite under 35 U.S.C. §112, second paragraph, with respect to "determining spatial similarity."

2D. The Examiner submits that the term "substantially equivalent" is a relative term which renders the claim indefinite. It is respectfully submitted that a search of issued patents revealed that the terminology "substantially equivalent" is present in 20,644 issued patents. In addition, for example, the terminology "substantially equivalent" is referred to in USPN 7,041,786 as follows:

> The term "***substantially equivalent***" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production.

Thus, it is respectfully submitted that, in similar fashion, it is clear to one skilled in the art that the terminology "substantially equivalent" in the present specification refers to a second structure having a sequence of atoms or atomic group of a molecule equivalent to that of a first structure having a sequence of atoms or atomic group of a molecule, where certain residues may be deleted or replaced without impairing the second structure's ability to perform a selected function of the first structure.

Hence, it is respectfully submitted that claims 13 and 24 are definite under 35 U.S.C. §112, second paragraph, with respect to the terminology "substantially equivalent."

REJECTION UNDER 35 U.S.C. §101:

In the Office Action, at pages 4-6, numbered paragraph 3, claims 13-15 and 24-26 were rejected under 35 U.S.C. §101, because the Examiner submitted that the invention lacks patentable utility. This rejection is traversed and reconsideration is requested.

It is respectfully submitted that the utility of the present invention is clear to one skilled in the art. For example, in Computer-Assisted Modeling, Contributions of Computational Approaches to Elucidating macromolecular Structure and Function, National Academy Press, Washington D.C., 1987:

p. 23 recites:

> As of mid-1987, more than 5,000 protein amino acid sequences had been reported, most of which were inferred from the DNA sequences that encode them. Although the collection is redundant (same protein from different species) and definitely biased (many human and few plant sequences, for example), several patterns nevertheless stand out. Foremost among these is that the number of different types of proteins is finite. It is becoming increasingly clear that most of the proteins determined thus far belong to identifiable families that are easily recognized by amino acid sequences alone. Indeed, the chances are now better than even that a newly determined amino acid sequence from a eukaryotic organism will be found to resemble a previously entered sequence. (emphasis added)
>
> Some of these families were anticipated (Table 3-1) on the basis of similarities in function and size. Thus, globins were all known to bind heme and to have very similar properties. We knew about large numbers of kinases, serine proteases, and thiol proteases, for example, and scores of protease inhibitors. It is not surprising, either, that many dehydrogenases and reductases have related sequences or that all the ATPases belong to a homologous set. (emphasis added)

p. 26 recites:

> The major data bases for sequences are the Protein Identification Resource (PIR) at the National Biomedical Research Foundation, Washington, D.C.; GebBank, operated by Bolt, Beranek, and Newman in Cambridge, Massachusetts; and EMBL Data Bank in Heidelberg, Germany (Table 3-2).

Hence, it is respectfully submitted that it is clear the present invention provides for determining amino acid sequences of unknown samples with a high degree of similarity to known amino acid sequences, thus enabling classification of the function of the unknown sample of an amino acid sequence into a grouping with the similar amino acid sequence.

There is no need to specify the particular function linked to the three-dimensional structure because is known to those skilled in the art that, for example, for specific amino acid sequences, certain functions are known. For example, as recited above, on page 23 of Computer-Assisted Modeling, Contributions of Computational Approaches to Elucidating

macromolecular Structure and Function,, Ibid., "globins were all known to bind heme and to have very similar properties."

Again the Examiner recites his theoretical example for which there is no basis - "if 3-D coordinates of an atomic group of a silicon semiconductor correlates with 3-D coordinates of an atomic group of a nucleic acid,..." It is respectfully submitted that those skilled in the art would proceed logically, as noted above, to compare unknown biological samples with known biological samples to obtain similarities between the structures of same so that functions of the unknown biological sample could be determined.

For example, on page 56, line 29 through page 57, line 10, the specification recites:

> FIG. 42 illustrates the constitution of a retrieval system that is made up of a data base 160 to which are registered three-dimensional structure data of proteins, a secondary structure calculation unit 161 that determines a secondary structure from the three-dimensional structure data in the data base 160 and divides it into partial structures, a secondary structure coordinate table 162 that stores the results obtained by the secondary structure calculation unit 161 as a type of the secondary structure and three-dimensional coordinates of points that constitute the type of the secondary structure, an input unit 163 that reads an input command of a user, a retrieving unit 164 that retrieves a similar structure based on the aforementioned method relying on the command that is input and the data in the secondary structure coordinate table, and a display unit 165 that graphically displays the retrieved result. Details of the units will now be described. (emphasis added)

It is clear that a data base is prepared with registered three-dimensional structure data of proteins, wherein, as is known to those skilled in the art, such information is generally available. The secondary structure calculation unit determines a secondary structure, divides it into subsets and stores the results. In one example, n amino acids are grouped into subsets (page 57, lines31-32 of the specification). Examples of types of secondary structures and their definitions are shown in Table I, page 58 of the specification. The operation of the retrieving unit is set forth on page 59 of the specification, and three-dimensional structures that are similar to known three-dimensional structures are retrieved from the data.

The Examiner submits that "the sets of three-dimensional coordinates are not limited to originate from two different structures, and the method may represent comparison of different groups of atoms of the same molecule. The specification does not disclose a utility for comparing different parts of the same compound or molecule and none is apparent." It is respectfully submitted that, as set forth above, subsets of a known structure are compared with subsets of the unknown structure, and if a similarity of a subset of a known structure with a subset of an unknown structure has a degree of similarity that is greater than a predetermined threshold value, the two subsets are determined to have a substantially similar function.

Thus, unknown samples may be classified, and their functions determined, which is an immediately useful result.

Thus, it is respectfully submitted that claims 13-15 and 24-26 are patentable 35 U.S.C. §101, and that claims 13-15 and 24-26 have patentable utility.

REJECTION UNDER 35 U.S.C. §112:

In the Office Action, at page 6, numbered paragraph 4, claims 13-15 and 24-26 were rejected under 35 U.S.C. §112, first paragraph, for the reasons set forth therein.

The Examiner submitted "since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

As noted above, it is clear to one skilled in the art that "most of the proteins determined thus far belong to identifiable families that are easily recognized by amino acid sequences alone." Hence, utilizing the present invention to determine that, for example, an amino acid sequence of a subset of an unknown sample has a degree of similarity that is greater than a threshold value for a known subset of an amino acid sequence would provide an identifiable family for the amino acid sequence of the subset of the unknown sample. A flow chart for the operations of the present invention is set forth above, and is submitted to be clear to one skilled in the art. The specifics of the operations are described in the specification, and are submitted to be clear. Hence, claims 13-15 and 24-26 of the claimed invention are submitted to be allowable under 35 U.S.C. §112, first paragraph, and to be supported by a specific, substantial and credible asserted utility and/or a well established utility for the reasons set forth above so that one skilled in the art would clearly know how to use the claimed invention.

REJECTION UNDER 35 U.S.C. §101:

In the Office Action, at page 6-8, numbered paragraph 5, claims 13-15 and 24-26 were rejected under 35 U.S.C. §101 because the Examiner asserted that the claimed invention is directed to non-statutory subject matter.

The Examiner submitted that the claims of the present invention do not provide a result that is specific, substantial and credible.

As noted above, for example, see claim 13 recites that a target molecule represented by a first point set and a sequence of atoms or atomic groups of atoms of a known molecule represented by a second point set are each divided into subsets. Now, we have two sets of subsets (known and unknown). Then, candidates for combination of correspondence are generated from the unknown subsets with respect to the known subsets based on restriction, an

rmsd is calculated for each candidate, a degree of spatial similarity between each candidate and respective known subset is determined, and if the degree of spatial similarity is greater than or equal to a predetermined threshold, the corresponding candidate has the same function as the known subset. Specific operations are set forth, for example, on pages 53-56 of the specification.

Further, those skilled in the art understand that the amino acid sequences in the example above are associated with specific functions (see in Computer-Assisted Modeling, Contributions of Computational Approaches to Elucidating macromolecular Structure and Function, Ibid.) The specification, on age 55 recites that the structural similarity of the two subsets may be judged by the three-dimensional structure matching method which accomplishes the correspondence among the elements of the two ordered point described in the "Analysis of Three-Dimensional Structure of Molecules I," and the rmsd among the points is calculated when an optimum matching is effected based on this method. A embodiment for refining the candidates and obtaining a decision of similarity between structure A and structure B is set forth on pages 55-56 of the specification.

Hence, the claimed method produces a result (a determination of a function of a sequence of atoms or atomic groups of atoms of a target molecule represented by a first point set). For example, for example, an amino acid sequence of the target molecule may be identified, thus identifying the function of the amino acid sequence. This is a useful, tangible and concrete result. Scientists use this result to determine structures of unknown biological materials, which facilitates scientific understanding of the functions of the structures.

It is respectfully submitted that, for example, as noted in Computer-Assisted Modeling, Contributions of Computational Approaches to Elucidating macromolecular Structure and Function, Ibid., the determination of amino acid sequences aids may be used in determination of identifiable families of proteins. Thus, the method set forth in claims 13-15 and 24-26 is a real world result and is useful.

Since determining a family of proteins to which a sequence of amino acid belongs enables one to ascertain the properties of the sequence, the present invention has a practical application that produces a real-world result, i.e., a tangible result is obtained.

As noted in Computer-Assisted Modeling, Contributions of Computational Approaches to Elucidating macromolecular Structure and Function, Ibid., for example, an amino acid sequence is associated with a particular function. For example, amino acid sequences constituting globins are all known to bind heme and to have very similar properties. Thus, there is evidence that the practical application of the invention produces a real-world result. Hence, a specific function need not be recited because the function is determined based on the amino acid sequence that is selected based on a degree of spatial similarity with a known amino acid sequence. Thus, the

claims produce a result that is specific, substantial and credible.

As noted above, using the operations of the claims of the present invention, an unknown structure can, for example, be determined to be a particular amino sequence. Since repeating the operations of the claims results in the same particular amino acid sequence, the claims are "concrete," i.e., the claims are directed to a result that can be substantially repeatable. It is respectfully submitted that the 3-D coordinates do not vary depending on the conditions of acquiring the coordinates. As in any controlled measuring system, the conditions for the biological sample are maintained the same for the known and unknown samples. Hence, a comparison of the measurements of the target biological sample will relate in the same manner each time to the measurements of the known biological sample. Those who are skilled in the art appreciate that the conditions of measurements of the unknown sample should be comparable to the conditions of measurements of the known samples. Thus, the Examiner's hypothesis that different conditions would be used is baseless.

Thus, it is respectfully submitted that claims 13-15 and 24-26 are patentable under 35 U.S.C. §101 because the claims are useful, tangible, and concrete and produce a real-world repeatable result that is specific, substantial and credible, the claims are directed to statutory subject matter, and the results obtained are within the statutory embodiments of the claims.

REJECTION UNDER 35 U.S.C. §102 AND §103:

In the Office Action, at page 6, numbered paragraph 4, claims 13-15 and 24-26 were rejected under 35 U.S.C. §102(b) as anticipated by Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991; hereafter, Flaherty) or Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992; hereafter, Mosimann) for the reasons set forth therein.

The Examiner submits that it is not clear what is not taught by Flaherty in the present invention. It should be noted that an invention is to be considered as a whole, not broken into portions and some portions located in different patents or articles and put together to "invent" the invention again. In Ruiz and Foundation v. A.B. Chance Company, 69 USPQ2d 1690 (CAFC January 29, 2004), the court held:

> In making the assessment of differences, section 103 specifically requires consideration of the claimed invention "as a whole." Inventions typically are new combinations of existing principles or features. Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698 (Fed. Cir. 1983) (noting that "virtually all [inventions] are combinations of old elements."). The "as a whole" instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result – often the very definition of invention.

> Section 103 precludes this hindsight discounting of the value of new combinations by requiring assessment of the invention as a whole. This court has provided further assurance of an "as a whole" assessment of the invention under § 103 by requiring a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would select the various elements from the prior art and combine them in the claimed manner. In other words, the examiner or court must show some suggestion or motivation, before the invention itself, to make the new combination. See In re Rouffet, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998).

It is respectfully submitted that Flaherty does not recite a method of analyzing, by a computer processor (Flaherty uses manual superimposition of structures), three-dimensional structures of sequences of atoms or atomic groups of molecules of biological substances, including a first structure of a sequence of atoms or an atomic group of a molecule of a first biological substance expressed by three-dimensional coordinates of elements belonging to a first point set and a second structure of a sequence of atoms or an atomic group of a molecule of a second biological substance expressed by three-dimensional coordinates of elements belonging to a second point set, comprising: dividing the second point set into a plurality of subsets each having a size that is determined by the size of the first point set; generating a combination of correspondence satisfying a restriction condition between the elements belonging to the first point set and the elements belonging to each of the subsets of the second point set from among all candidates for the combination of correspondence (Flaherty inspects by eye to guide classifications); and calculating a root mean square distance between the elements corresponding in the combination of correspondence generated (Flaherty uses empirical identification of equivalent residues in preference to computation methods that rely primarily on distance criteria), wherein the restriction condition includes a condition such that an attribute value of each of the elements belonging to the first point set coincides with an attribute value of the corresponding element belonging to the second point set in a candidate for combination of correspondence, determining if a degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to a predetermined threshold degree of similarity (Flaherty specifies amino acid residues by a one letter code, aligns equivalent amino acid residues in the molecules above each other and indicates same by uppercase letters; lowercase letters identify residues in the sequence that are not considered equivalent); and outputting a determination, if the degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to the predetermined threshold degree of similarity, that a function of the first structure of the sequence of atoms or the atomic group of the molecule of the

first biological substance is substantially equivalent to a function of the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance (Flaherty generates a C_α stereo plot and visually compares the structures - see FIG. 2 of Flaherty), as is recited in independent claim 13 of the present invention.

In addition, Flaherty does not recite a method of analyzing, by a computer, three-dimensional structures of sequences of atoms or atomic groups of molecules of biological substances (Flaherty uses manual superimposition of structures) including a first structure of a sequence of atoms or an atomic group of a molecule of a first biological substance expressed by three-dimensional coordinates of elements belonging to a first point set and a second structure of a sequence of atoms or an atomic group of a molecule of a second biological substance expressed by three-dimensional coordinates of elements belonging to a second point set, comprising: dividing the second point set into a plurality of subsets each having a size that is determined by the size of the first point set; generating a combination of correspondence such that an attribute value of each of the elements belonging to the first point set coincides with an attribute value of the corresponding element belonging to the each of the subsets of the second point set from among all candidates for the combination of correspondence (Flaherty inspects by eye to guide classifications); calculating a root mean square distance (rmsd) between the elements corresponding in the combination of correspondence generated, and where the rmsd is less than a predetermined threshold value, determining that the elements of the first point set coincide with or are similar to the subset of the second point set corresponding in the combination of correspondence generated and storing a correspondence/similarity determination on a computer readable recording medium (Flaherty uses empirical identification of equivalent residues in preference to computation methods that rely primarily on distance criteria), determining if a degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to a predetermined threshold degree of similarity (Flaherty specifies amino acid residues by a one letter code, aligns equivalent amino acid residues in the molecules above each other and indicates same by uppercase letters; lowercase letters identify residues in the sequence that are not considered equivalent); and outputting a determination, if the degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to the predetermined threshold degree of similarity, that a function of the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance is substantially equivalent to a function of the second structure of the sequence of atoms or the

atomic group of the molecule of the second biological substance (Flaherty generates a C_α stereo plot and visually compares the structures - see FIG. 2 of Flaherty), as is recited in independent claim 24 of the present invention.

In contrast, Flaherty utilized an iterative manual process of superimposing the structures of actin and HSC70 ATPase fragment, wherein the superimposed molecules were superimposed and inspected by eye to guide classifications of C_α positions into equivalent positions. Clearly, the Flaherty process is very different from, more time-consuming than, and more manual than the operations of the method of the present invention. No manual alignment is made in the present claimed invention.

Thus, it is respectfully submitted that independent claims 13 and 24 of the present invention are not anticipated under 35 U.S.C. §102(B) by Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991). Since claims 14-15 and 25-26 depend from independent claims 13 and 24, respectively, claims 14-15 and 25-26 are not anticipated under 35 U.S.C. §102(B) by Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991) for at least the reasons that claims 13 and 24 are not anticipated under 35 U.S.C. §102(B) by Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991).

It is respectfully submitted that Mosimann does not recite a method of analyzing, by a computer processor, three-dimensional structures of sequences of atoms or atomic groups of molecules of biological substances (Mosimann uses structures that have already been obtained and simply manually aligns them using inspection by eye to determine similarities), including a first structure of a sequence of atoms or an atomic group of a molecule of a first biological substance expressed by three-dimensional coordinates of elements belonging to a first point set and a second structure of a sequence of atoms or an atomic group of a molecule of a second biological substance expressed by three-dimensional coordinates of elements belonging to a second point set, comprising: dividing the second point set into a plurality of subsets each having a size that is determined by the size of the first point set; generating a combination of correspondence satisfying a restriction condition between the elements belonging to the first point set and the elements belonging to each of the subsets of the second point set from among all candidates for the combination of correspondence (Mosimann manually aligns the known amino acid sequences and inspects by eye); and calculating a root mean square distance between the elements corresponding in the combination of correspondence generated, wherein the restriction condition includes a condition such that an attribute value of each of the elements belonging to the first point set coincides with an attribute value of the corresponding element belonging to the second point set in a candidate for combination of correspondence (After Mosimann aligns the amino acid sequences, the rmsd is calculated for confirmation), determining if a degree of spatial similarity between the first structure of the sequence of atoms

or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to a predetermined threshold degree of similarity (Mosimann revises the alignment based on inspection of the P-30 sequence fitted into the RNase A structure); and outputting a determination, if the degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to the predetermined threshold degree of similarity, that a function of the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance is substantially equivalent to a function of the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance (Mosimann revises the alignment based on inspection of the P-30 sequence fitted into the RNase A structure), as is recited in independent claim 13 of the present invention.

The three-dimensional structure of bovine pancreatic RNase A is known, and the complete amino acid sequence of P-30 has been published (PROTEINS:Structure, Function, and Genetics, Mosimann et al., p. 392). Hence, Mosimann does not describe operations of obtaining amino acid sequences, as are set forth in claim 13 of the present invention. Mosimann recites a two-step process. First, automated alignment programs are used to align the amino acid sequences of the P-30 protein and the bovine pancreatic RNase, and subsequently a revision of the alignment based on inspection of the P-30 sequence fitted into the RNase A structure (PROTEINS:Structure, Function, and Genetics, Mosimann et al., p. 393). Clearly, Mosimann does not set forth the operations of claim 13 of the present invention.

In addition, Mosimann does not recite a method of analyzing, by a computer, three-dimensional structures of sequences of atoms or atomic groups of molecules of biological substances (Mosimann uses structures that have already been obtained and simply manually aligns them using inspection by eye to determine similarities)including a first structure of a sequence of atoms or an atomic group of a molecule of a first biological substance expressed by three-dimensional coordinates of elements belonging to a first point set and a second structure of a sequence of atoms or an atomic group of a molecule of a second biological substance expressed by three-dimensional coordinates of elements belonging to a second point set, comprising: dividing the second point set into a plurality of subsets each having a size that is determined by the size of the first point set; generating a combination of correspondence such that an attribute value of each of the elements belonging to the first point set coincides with an attribute value of the corresponding element belonging to the each of the subsets of the second point set from among all candidates for the combination of correspondence (Mosimann manually aligns the known amino acid sequences and inspects by eye); calculating a root mean square

distance (rmsd) between the elements corresponding in the combination of correspondence generated, and where the rmsd is less than a predetermined threshold value (After Mosimann aligns the amino acid sequences, the rmsd is calculated for confirmation), determining that the elements of the first point set coincide with or are similar to the subset of the second point set corresponding in the combination of correspondence generated and storing a correspondence/similarity determination on a computer readable recording medium, determining if a degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to a predetermined threshold degree of similarity (Mosimann revises the alignment based on inspection of the P-30 sequence fitted into the RNase A structure); and outputting a determination, if the degree of spatial similarity between the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance and the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance is greater than or equal to the predetermined threshold degree of similarity, that a function of the first structure of the sequence of atoms or the atomic group of the molecule of the first biological substance is substantially equivalent to a function of the second structure of the sequence of atoms or the atomic group of the molecule of the second biological substance (Mosimann revises the alignment based on inspection of the P-30 sequence fitted into the RNase A structure), as is recited in independent claim 24 of the present invention.

In contrast, Mosimann recites a comparative molecular model of P-30 protein constructed based on the known three-dimensional structure of bovine pancreatic RNase, wherein, in the modeling procedure, automatic sequence alignments were revised based upon the inspection of the RNase A structure before the amino acids of the P-30 protein were assigned the coordinates of the RNase A template, intermolecular steric clashes were relieved on an interactive graphics device through the adjustment of side chain torsion angles, and energy minimizing of the model to optimize stereochemistry and relieve any remaining unacceptably close contacts (see Abstract, Mosimann et al.). Clearly, Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992) does not anticipate independent claims 13 and 24 of the present claimed invention under 35 U.S.C. §102(b). Since claims 14-15 and 25-26 of the present invention depend from independent claims 13 and 24, respectively, claims 14-15 and 25-26 are not anticipated by Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992) under 35 U.S.C. §102(b) for at least the reasons independent claims 13 and 24 are not anticipated by Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992) under 35 U.S.C. §102(b).

Hence, it is respectfully submitted that the Examiner's position that the instant claims are

drawn to a method of analyzing three-dimensional structures by generating correspondence between set points describing two three-dimensional structures and calculating root mean square distance between the corresponding elements, and that the claims read on any reference teaching comparison of two three dimensional structures and calculating rmsd therefor is incorrect. Clearly, as described above, Flaherty does not calculate rmsd to determine similarity of amino acid sequences, but relies on manual superposition and evaluation by eye. Mosimann does not rely on rmsd calculations to determine amino acid sequence similarity, but rather begins with known amino acid sequences of two samples, uses alignment programs for lining up similar amino acid sequences, and then revises the alignment based on visual inspection. Mosimann merely calculates rmsd after determining alignment for corroboration. Hence, neither Flaherty nor Mosimann teaches or suggests the operations of claims 13-15 and/or 24-26 of the present invention. Thus, claims 13-15 and 24-26 of the present invention are submitted not to be anticipated under 35 U.S.C. §102(b) by Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991) or Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992) and are submitted to be patentable under 35 U.S.C. §103(a) over Flaherty et al. (Proc. Natl. Acad. Sci. USA, 88, 5041-5045, 1991) and/or Mosimann et al. (Proteins: Structure, Function and Genetics, 14, 392-400, 1992), alone or in combination.

DOUBLE PATENTING:

In the Office Action, at pages 9-10, numbered paragraph 7, claims 13-15 and 24-25 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16, 17 of co-pending application 09/909,809 or claims 5-11, 24 of co-pending application 09/910,054.

Since U.S. Patent Application Nos. 09/909,809 and 09/910,054 have not yet been issued as patents, and since the all of the claims of the instant application have not yet been indicated as allowable except for the provisional rejection, it is believed that any submission of a Terminal Disclaimer or arguments as to the non-obvious nature of the claims would be premature. MPEP 804(I)(B). As such, it is respectfully requested that the applicants be allowed to address any obviousness-type double patenting issues remaining once the rejections of the claims under 35 U.S.C. §101, §112 (first and second paragraphs), §102 and §103 are resolved or on allowance of U.S. Patent Application Nos. 09/909,809 and/or 09/910,054.

CONCLUSION:

In accordance with the foregoing, it is respectfully submitted that all outstanding objections and rejections have been overcome and/or rendered moot, and further, that all pending claims patentably distinguish over the prior art. Thus, there being no further

outstanding objections or rejections, the application is submitted as being in condition for allowance which action is earnestly solicited.

If the Examiner has any remaining issues to be addressed, it is believed that prosecution can be expedited by the Examiner contacting the undersigned attorney for a telephone interview to discuss resolution of such issues.

If there are any underpayments or overpayments of fees associated with the filing of this Amendment, please charge and/or credit the same to our Deposit Account No. 19-3935.

Respectfully submitted,

STAAS & HALSEY LLP

Date: July 5, 2006 By: Darleen J. Stockley

Darleen J. Stockley
Registration No. 34,257

1201 New York Avenue, N.W.
Suite 700
Washington, D.C. 20005
Telephone: (202) 434-1500
Facsimile: (202) 434-1501